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Elevated skin and core temperatures both contribute to reductions in tolerance to a simulated haemorrhagic challenge

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Abstract

Tolerance to a simulated haemorrhagic insult, such as lower-body negative pressure (LBNP), is profoundly reduced when accompanied by whole-body heat stress. The aim of this study was to investigate the separate and combined influence of elevated skin (T_{skin}) and core temperatures (T_{core}) on LBNP tolerance. We hypothesized that elevations in T_{skin} as well as T_{core} would both contribute to reductions in LBNP tolerance and that the reduction in LBNP tolerance would be greatest when both T_{skin} and T_{core} were elevated. Nine participants underwent progressive LBNP to presyncope on four occasions, as follows: (i) control, with neutral T_{skin} (34.3 ± 0.5°C) and T_{core} (36.8 ± 0.2°C); (ii) primarily skin hyperthermia, with high T_{skin} (37.6 ± 0.2°C) and neutral T_{core} (37.1 ± 0.2°C); (iii) primarily core hyperthermia, with neutral T_{skin} (35.0 ± 0.5°C) and high T_{core} (38.3 ± 0.2°C); and (iv) combined skin and core hyperthermia, with high T_{skin} (38.8 ± 0.6°C) and high T_{core} (38.1 ± 0.2°C). The LBNP tolerance was quantified via the cumulative stress index (in millimetres of mercury × minutes). The LBNP tolerance was reduced during the skin hyperthermia (569 ± 151 mmHg min) and core hyperthermia trials (563 ± 194 mmHg min) relative to control conditions (1010 ± 246 mmHg min; both $P < 0.05$). However, LBNP tolerance did not differ between skin hyperthermia and core hyperthermia trials ($P = 0.92$). The lowest LBNP tolerance

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Competing interests
None declared.

Author contributions
All experiments took place at the Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas, TX, USA. J.P. and C.G.C. contributed to conception and design of the experiments. J.P., C.G.C., R.A.I.L., Z.J.S. and D.G. contributed to acquisition, analysis and/or interpretation of data and experimental results. J.P., R.A.I.L., Z.J.S., D.G. and C.G.C. contributed to drafting the work or revising it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

was observed during combined skin and core hyperthermia(257±106mmHgmin; $P<0.05$ relative to all other trials). These data indicate that elevated skin temperature, as well as elevated core temperature, can both contribute to reductions in LBNP tolerance in heat-stressed individuals. However, heat stress-induced reductions in LBNP tolerance are greatest in conditions when both skin and core temperatures are elevated.

Introduction

Whole-body heat stress increases skin and body core temperatures, resulting in elevations in skin blood flow, via both neurally mediated (i.e. reflex; Roddie *et al.* 1957; Johnson *et al.* 1976) and locally mediated cutaneous vasodilatation (i.e. direct; Kellogg *et al.* 1999), along with parallel reductions in central blood volume (Rowell *et al.* 1969; Minson *et al.* 1998; Crandall *et al.* 2008). Such increases in skin blood flow, coupled with insufficient cutaneous vasoconstriction during progressive central hypovolaemia (Crandall *et al.* 2010; Pearson *et al.* 2013), are problematic for the maintenance of arterial blood pressure. The resultant effect is a profound reduction in tolerance to a simulated haemorrhagic challenge, such as progressive lower-body negative pressure (LBNP) to presyncope (Lind *et al.* 1968; Allan & Crossley, 1972; Johnson *et al.* 1973; Wilson *et al.* 2006; Keller *et al.* 2009).

When heat stress-induced reductions in central blood volume are countered via rapid saline/dextran infusion during the heat stress, LBNP tolerance is returned to non-heat stress levels (Keller *et al.* 2009). Likewise, the cardiovascular responses to a mild subpresyncopal orthostatic challenge are improved when skin temperature is returned to normothermic values (Lucas *et al.* 2010) or reduced below normothermic values (Wilson *et al.* 2002). These improvements with skin-surface cooling were associated with increased arterial blood pressure, perhaps owing in part to a transfer of blood volume from the skin to the central vasculature. Furthermore, a slightly lower skin temperature modestly improved LBNP tolerance in hyperthermic individuals following exercise (Pearson *et al.* 2014), although in that protocol skin temperatures were still elevated above normothermic values, and a normothermic reference LBNP challenge was not imposed. It is unknown whether returning skin surface temperatures to normothermic values, without actively lowering skin temperature below normothermic values, would return LBNP tolerance to that observed with a normothermic LBNP challenge, despite core temperature remaining elevated. That is, given the parallel effects of skin temperature on skin blood flow, and the presumed reciprocal effect on central blood volume, reducing skin surface temperature in heat-stressed individuals may therefore normalize LBNP tolerance, despite core temperature remaining elevated. However, little is known regarding the role of primarily skin hyperthermia *versus* primarily core hyperthermia on LBNP tolerance. The latter conditions may occur during exercise with adequate evaporative cooling of the skin surface, resulting in elevated core temperatures with relatively normothermic skin temperatures, whereas the former conditions may be experienced during brief passive exposure to high environmental temperatures. Investigating the effect of separate and combined increases in skin and core temperature upon LBNP tolerance may provide insight towards the treatment of heat-stressed individuals who are experiencing a haemorrhagic challenge. Therefore, the aim of this study was to examine the separate and combined influences of increased skin and body core temperatures

upon tolerance to a simulated haemorrhagic challenge. Specifically, we hypothesized that LBNP tolerance would be reduced when skin temperature is primarily elevated (with minimal accompanying increases in core temperature), as well as when core temperature is primarily elevated (with minimal accompanying increases in skin temperature). Furthermore, we hypothesized that the greatest reduction in LBNP tolerance would occur with combined increases in skin and core temperatures.

Methods

Ethical approval

Nine subjects (eight men) participated in this study. Subject characteristics (mean ± SD) were as follows: age, 29 ± 5 years; height, 184± 12 cm; and weight, 82.3 ± 13.2 kg. The one female participant was tested in the follicular phase of the menstrual cycle for all trials. Subjects were not taking medications, were non-smokers, were free of any known cardiovascular, metabolic or neurological diseases and refrained from alcohol, caffeine and exercise for 24 h before the study. Subjects were informed of the purpose, procedures and risks of the study before providing their informed written consent. The protocol and consent were approved by the institutional review boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas (reference number: STU 0602011-099). The study conformed to the standards set by the *Declaration of Helsinki*.

Instrumentation and experimental protocol

On experimental days, adequate hydration was confirmed via urine specific gravity (<1.020), measured using a digital refractometer. Approximately 2 h before the onset of data collection, subjects swallowed an ingestible telemetry pill for the measurement of core (intestinal) temperature (HQ, Palmetto, FL, USA). Subjects voided their bladder before nude body mass was recorded, which was also obtained after each trial to provide an indication of fluid loss. Height was measured using a stadiometer. Mean skin temperature was measured from the weighted average temperature across six sites (Taylor *et al.* 1989) using thermocouples fixed to the skin with porous adhesive tape. Arterial blood pressure was continuously measured non-invasively using photoplethysmography (Finometer Pro; FMS, Amsterdam, The Netherlands), while intermittent blood pressure was obtained via auscultation of the brachial artery (Tango; Suntech Medical Instruments, Raleigh, NC, USA). Heart rate was obtained from an ECG (Agilent, Munich, Germany) that was interfaced with a cardiotachometer (1000 Hz sampling rate; CWE, Ardmore, PA, USA). Cardiac output and stroke volume were measured using a foreign gas rebreathing system (Innovision A/S, Odense, Denmark). Mean blood flow velocity in the right middle cerebral artery served as an index of cerebral perfusion, which was measured using 2 MHz pulsed Doppler ultrasound (Multiflow; DWL Elektronische Systeme, Singen, Germany). The Doppler probe was maintained in position throughout the protocol using a commercially available headpiece. The partial pressure of end-tidal carbon dioxide ($P_{\mathrm{ET,CO_2}}$) was sampled from a nasal cannula connected to a capnograph (9004 Capnocheck® Plus; Smiths Medical International Ltd, Watford, UK).

Skin blood flow was measured from the dorsal forearm via laser Doppler probes (Periflux413; Perimed, North Royalton, OH, USA) connected to a laser-Doppler flowmeter (Periflux5010; Perimed). Probes were fitted inside a local heating device (Peritemp 4005; Perimed) capable of controlling local skin temperature at that site. The local heater and laser Doppler probe assembly was placed over a fine-wire skin thermocouple (RET-4, Type T thermocouple; Physitemp Instruments Inc., Clifton, NJ, USA). Local heaters were continually adjusted to match mean skin temperatures under the water-perfused suit. At the end of each trial, local heat-induced maximal skin blood flow was assessed via 30 min of local heating at 42°C measured at the skin and local heater interface.

Following instrumentation, subjects rested in the supine position for 30 min to allow for the stabilization of fluid shifts. Baseline data were subsequently obtained. Subjects were then exposed to one of four trials, on separate days and in a randomized order. Of these four trials, one was a control trial, in which skin and core temperatures remained at neutral levels throughout the protocol. The three remaining trials were designed to elicit either an increase in primarily skin temperature (skin hyperthermia), primarily core temperature (core hyperthermia) or both skin and core temperatures (combined skin and core hyperthermia). Each trial was separated by at least 3 days. To obtain the desired skin and core temperatures, subjects donned a water-perfused tube-lined suit (Med-Eng, Ottawa, ON, Canada) that covered their entire body except for the head, hands, feet and the left forearm, on which skin blood flow was measured. The suit permitted the control of whole-body skin and core temperatures by adjusting the temperature of the water perfusing the suit.

During the control trial, 34°C water was perfused through the suit. During the three trials where either skin or core temperatures were increased, subjects were exposed to slightly different heating protocols before the onset of a simulated haemorrhagic challenge (LBNP). During the skin hyperthermia trial, water at 48–50°C was perfused through the suit to elevate skin temperatures quickly to ~38°C while limiting increases in core temperature. This period of heating, lasting between 20 and 25 min, was immediately followed by the LBNP challenge. During the core hyperthermia trial, water at 48–50°C was perfused through the suit, elevating skin temperatures to ~38°C. This period of heating was sustained for ~50 min, resulting in an increase in core temperature of ~1.2°C. Upon reaching this increase in core temperature, the temperature of the water perfusing the suit was reduced to ~10°C for ~6 min and thereafter held at ~37°C to return skin temperatures to baseline values (~34–35°C), while minimizing decreases in core temperature. The LBNP challenge then ensued. During the skin and core hyperthermia trial, water at 48–50°C was perfused through the suit, elevating skin temperatures to ~38°C. This period of heating was sustained for ~50 min, resulting in an increase in core temperature of ~1.2°C, after which subjects underwent the LBNP challenge. In each trial, all measurements were obtained at the end of the heating protocol specific to that trial, immediately before the onset of LBNP.

For all trials, LBNP began at 20 mmHg for 3 min, followed by increasing negative pressure by 10 mmHg in 3 min stages until presyncope. The termination of LBNP was based upon the subject self-reporting of feeling faint and/or nauseous, a rapid and progressive decrease in blood pressure resulting in sustained systolic blood pressure of <80 mmHg and/or a relative and pronounced bradycardia. Throughout LBNP, arterial blood pressures were also

measured at the brachial artery by automated auscultation (Tango; Suntech Medical Instruments). Tolerance to LBNP was quantified using the cumulative stress index (CSI; Luft *et al.* 1976), calculated by summing the time at each level of LBNP multiplied by LBNP level (i.e. 20 mmHg × 3 min + 30 mmHg × 3 min + 40 mmHg × 3 min, etc.) until presyncope.

Data analysis

Temperature and haemodynamic data were collected via a data-acquisition system (Biopac Systems Inc., Santa Barbara, CA, USA). Data were averaged across 60 s at baseline and after the desired increase in core and mean skin temperatures prior to LBNP. Cardiac output and stroke volume were measured at normothermic baseline and before the onset of LBNP in each trial. Skin blood flow is reported as cutaneous vascular conductance [in arbitrary units (a.u.) per millimetre of mercury], calculated as skin blood flow units (in arbitrary units) divided by mean arterial pressure (in millimetres of mercury). Changes in cutaneous vascular conductance during LBNP are expressed as a percentage of the maximal cutaneous vascular conductance values obtained after 30 min of local heating. To express data throughout LBNP of varying durations between trials, thermal data during LBNP were averaged over a 30 s period immediately preceding 20, 40, 60 and 80% of maximal CSI, as well as during a 15 s period immediately preceding the termination of LBNP (i.e. presyncope).

With the exception of CSI, data were statistically analysed using a two-way repeated-measures ANOVA with main factors of thermal condition (control, skin hyperthermia, core hyperthermia and combined skin and core hyperthermia) and time. Analysis of body temperatures was completed with levels for time of baseline, pre-LBNP, 20, 40, 60 and 80% CSI, and presyncope. Analysis of blood pressure and cutaneous vascular conductance responses was completed with levels of time of baseline, pre-LBNP, 90, 80, 70, 60, 50, 40, 30, 20 and 10 s prior to presyncope, and presyncope). These data were analysed during the final 90 s prior to presyncope and cessation of LBNP in order to examine the cutaneous vascular responses to arterial baroreceptor unloading in all trials. The CSI data were analysed via one-way repeated-measures ANOVA. *Post hoc* analyses were performed using repeated-sampling corrected paired *t* tests (Bonferroni). Data were analysed using GraphPad Prism (version 6; GraphPad Software, Inc., La Jolla, CA, USA) and SPSS v20 (IBM, Armonk, NY, USA), with *a priori* statistical significance set at $P < 0.05$. Data are reported as mean values ± SD.

Results

Skin and core temperature responses for each trial are depicted in Fig. 1. At baseline, mean skin and core temperatures were not different between trials (all $P > 0.05$). During the control trial, mean skin and core temperatures did not change from baseline throughout LBNP (both $P > 0.05$). During the core hyperthermia trial, mean skin temperatures were similar to baseline values prior to and throughout LBNP (all $P > 0.05$). Mean skin temperatures were increased at pre-LBNP, relative to baseline, during both the skin hyperthermia and the combined skin and core hyperthermia trials (both $P < 0.05$) and

remained greater throughout LBNP relative to control and core hyperthermia trials (all $P < 0.05$). By experimental design, forearm skin temperatures at the location of the laser-Doppler probe followed the changes in mean skin temperature during each trial.

During the skin hyperthermia trial, core temperature increased slightly throughout LBNP such that it was greater relative to the control trial ($P < 0.001$). By design, core temperature was elevated during the core hyperthermia and combined skin and core hyperthermia trials, and remained greater throughout LBNP during these trials relative to the control and skin hyperthermia trials (all $P < 0.05$). In the latter stages of LBNP, core temperature declined slightly during the core hyperthermia trial and was lower relative to the combined skin and core hyperthermia trial ($P < 0.05$).

Tolerance to the LBNP challenge during each trial is depicted in Fig. 2. The LBNP tolerance was greatest during the control trial (1010 ± 246 mmHg min, $P < 0.001$) relative to both the skin hyperthermia (569 ± 151 mmHg min) and core hyperthermia trials (563 ± 194 mmHg min; both $P < 0.05$). However, despite large differences in skin and core temperatures, LBNP tolerance was not different between skin hyperthermia and core hyperthermia trials ($P = 0.92$). The lowest LBNP tolerance occurred during the combined skin and core hyperthermia trial (257 ± 106 mmHg min; $P < 0.001$ relative to all other trials).

Cutaneous vascular conductance responses are shown in Fig. 3. Prior to LBNP, cutaneous vascular conductance was not different between the combined skin and core hyperthermia (89 ± 14% max), skin hyperthermia (77 ± 14% max) and core hyperthermia trials (76 ± 11% max, all $P > 0.05$), while each was greater than cutaneous vascular conductance in the control trial (23 ± 14% max; all $P < 0.01$). At presyncope, cutaneous vascular conductance was reduced slightly relative to pre-LBNP during the control trial (−8 ± 46% max), although the variability of this response was fairly large. The magnitude of reduction in cutaneous vascular conductance, from pre-LBNP to presyncope, did not differ between the combined skin and core hyperthermia (−12 ± 14% max) and skin hyperthermia trials (−6 ± 34% max, $P \pm = 0.73$). During the core hyperthermia trial, cutaneous vascular conductance decreased by 65 ± 8% max from pre-LBNP to presyncope ($P < 0.05$ relative to all other trials) as a result of the combined effect of reduced skin temperature and LBNP.

Haemodynamic responses are shown in Table 1. Cardiac output was not different between trials at baseline (all $P > 0.05$) but increased in all thermal trials at pre-LBNP (all $P < 0.05$). Changes in heart rate, middle cerebral blood velocity and $P_{\mathrm{ET,CO_2}}$ in response to LBNP were not different between trials (all $P > 0.05$). Mean arterial pressure decreased during LBNP in all trials (all $P < 0.05$; Fig. 4), was slightly lower during LBNP in the combined skin and core hyperthermia trial relative to all other trials, yet was not different between trials at baseline, pre-LBNP and presyncope (all $P > 0.05$).

Body weight was reduced following the skin hyperthermia, core hyperthermia and combined skin and core hyperthermia trials (−0.9 ± 0.3, − 1.9 ± 0.7 and −2.1 ± 0.7% body mass, respectively) relative to the control trial, where body weight was unchanged (all $P < 0.05$). The magnitude of body weight loss was greatest during the core hyperthermia and combined skin and core hyperthermia trials relative to the skin hyperthermia trial (both $P < 0.05$),

while there was no difference in body weight loss between core hyperthermia and combined skin and core hyperthermia trials ($P = 0.50$).

Discussion

The aim of this study was to investigate the separate and combined contributions of elevated skin and core temperatures on LBNP tolerance during heat stress. As expected, combined elevations in skin and core temperature with passive heat stress greatly reduced LBNP tolerance relative to the control conditions. Although primarily skin hyperthermia and primarily core hyperthermia both reduced LBNP tolerance relative to the control trial, LBNP tolerance was not different between these separate hyperthermic conditions. These data demonstrate that elevations in skin and core temperatures that are primarily separate from one another can both contribute to impaired LBNP tolerance during passive heat stress. Interestingly, the similar reduction in LBNP tolerance with increases in either primarily skin or primarily core temperature occurred despite a markedly different cutaneous vascular conductance during the LBNP challenge between these trials.

Hyperthermia and LBNP tolerance

Whole-body heat stress increases both skin and core body temperatures, which is accompanied by cutaneous vasodilatation that, in extreme conditions, can increase skin blood flow upwards of 7 l min^{-1} (Rowell *et al.* 1969). It is well established that whole-body passive heat stress severely compromises LBNP tolerance (Lind *et al.* 1968; Allan & Crossley, 1972; Johnson *et al.* 1973; Wilson *et al.* 2006; Keller *et al.* 2009). Prior to the present study, however, the primarily separate contribution of elevated skin and core temperatures to this reduced LBNP tolerance was unknown. As expected, we observed substantially lower LBNP tolerance when skin and core temperatures were simultaneously elevated by whole-body passive heat stress (Fig. 2). The LBNP tolerance was also reduced by increases in primarily skin temperature, as well as increases in primarily core temperature (Fig. 2). These data indicate that LBNP tolerance is reduced to a similar extent regardless of whether heat stress results primarily in elevated skin or core temperature, although a further reduction in LBNP tolerance occurred when both were elevated simultaneously. Taken together, these data suggest that elevated skin and core temperatures can both contribute to a compromised LBNP tolerance during heat stress, but when elevations in skin and core temperature are combined the reduction in LBNP tolerance is even further compromised.

Compromised LBNP tolerance in heat-stressed individuals has been attributed, in part, to reduced central blood volume (Keller *et al.* 2009) and an increased skin blood flow (Rowell *et al.* 1969; Minson *et al.* 1998; Crandall *et al.* 2008) coupled with insufficient cutaneous vasoconstriction during LBNP (Crandall *et al.* 2010; Pearson *et al.* 2013). Prior to LBNP, mean skin temperatures and cutaneous vascular conductance were elevated to a similar extent between the skin hyperthermia and combined skin and core hyperthermia trials. Though speculative, these observations suggest that reductions in central blood volume that accompany cutaneous vasodilatation (Rowell *et al.* 1969; Minson *et al.* 1998; Crandall *et al.* 2008) were also likely to be similar between these two trials. However, central blood volume was not measured in the present study to confirm this speculation. Furthermore, the

reduction in cutaneous vascular conductance at presyncope was rather minimal (~ 6–12%) and not different between these two trials. Despite these important similarities, the reduction in LBNP tolerance was greater in the combined skin and core hyperthermia trial relative to the skin hyperthermia trial (Fig. 3). The LBNP tolerance was not different between the core hyperthermia and skin hyperthermia trials, despite a far greater reduction in cutaneous vascular conductance during the LBNP challenge in the core hyperthermia trial (45 *versus* 8%, respectively; Fig. 3). These data suggest that the level of cutaneous vasodilatation prior to LBNP and/or the reductions in cutaneous vascular conductance during LBNP may have only a minimal influence on LBNP tolerance in the thermal conditions investigated herein, and/or different mechanisms may be responsible for the reduction in LBNP tolerance between these thermal trials. This suggestion is in contrast to previous data suggesting that an insufficient cutaneous vasoconstriction whilst arterial blood pressure declines may be a leading factor contributing to impaired LBNP tolerance in heat-stressed individuals (Crandall *et al*. 2010; Pearson *et al*. 2013). Although speculative, this apparent contrast suggests that the changes in central blood volume and cutaneous vascular conductance during heat stress may not share a linear relationship. That is, during LBNP the central blood volume declines owing to blood pooling in the lower limbs; however, if central blood volume was different before the onset of LBNP between the different thermal conditions, this may help to explain differences in tolerance between conditions despite similarities or differences in cutaneous vascular conductance responses between these trials. Central blood volume was not measured in this study and therefore we do not know how it was influenced prior to and during LBNP between the different thermal trials. In order to understand more fully the influence of cutaneous vascular conductance upon arterial blood pressure regulation during a combined heat stress and haemorrhagic challenge and to reconcile the present data with the aforementioned proposed hypotheses (Crandall *et al*. 2010; Pearson *et al*. 2013), it may be necessary to measure central blood volume during similar trials.

In heat-stressed individuals, cooling of the skin surface improves the cardiovascular and cerebrovascular responses during subpresyncopal upright tilt testing (Wilson *et al*. 2002) and LBNP (Lucas *et al*. 2010), relative to when skin surface temperature remains elevated. These improved haemodynamic responses are presumably attributable to decreases in skin temperature and accompanying cutaneous vasoconstriction, which return skin blood flow toward baseline values, thereby enabling a prolonged maintenance of central blood volume, arterial blood pressure and cerebral blood flow. Such responses would suggest a greater capacity to withstand a haemorrhagic insult when skin surface temperature is actively reduced below typical normothermic values (~34°C). Consistent with this suggestion, the present study showed that LBNP tolerance improved relative to the combined skin and core hyperthermia trial when skin temperature was returned to control values during the core hyperthermia trial. That said, despite a lowered cutaneous vascular conductance accompanying reduced skin temperature in the core hyperthermia trial, LBNP tolerance was similar to the skin hyperthermia trial where skin temperatures and cutaneous vascular conductance were higher throughout LBNP. Furthermore, LBNP tolerance was reduced during the core hyperthermia trial relative to the control trial (Fig. 2), despite no difference in cutaneous vascular conductance across the final 80 s of LBNP between these two trials (Fig. 3). These findings suggest that if core temperature remains elevated, returning the skin

to a neutral temperature may not be sufficient to preserve LBNP tolerance completely relative to thermoneutral conditions. Therefore, these observations suggest that in a heated individual the skin surface needs to be cooled perhaps to levels lower than normothermic skin temperatures to restore tolerance to a haemorrhagic challenge relative to when the individual is in a thermoneutral state.

Each thermal trial caused a greater reduction in body mass compared with the control trial. Furthermore, body mass loss was greatest during the core hyperthermia and combined skin and core hyperthermia trials relative to the skin hyperthermia trial (~1.9%, 2.1% and 0.9% body mass, respectively). Differences in body mass loss were likely to be a result of differences in sweat loss owing to the different duration of passive heat stress necessary to create the applied thermal conditions, in combination with minimal increases in core temperature during the skin hyperthermia trial. Fluid loss associated with heat stress can influence tolerance to a simulated haemorrhagic challenge. We previously reported that passive heat stress-induced reductions in total body water of ~1.6% body mass reduced LBNP tolerance by ~225 CSI units relative to conditions in which fluid loss was prevented (Lucas *et al.* 2013). Given this observation, it is unlikely that the small reductions in total body water can account for the observed reductions in LBNP tolerance during the skin hyperthermia trial relative to the control trial. It is noteworthy that reductions in body mass between core hyperthermia and combined skin and core hyperthermia were similar despite a significant difference in LBNP tolerance between these trials. Therefore, although body mass loss primarily owing to sweat loss may explain some of the decrease in tolerance between thermal trials, its impact upon LBNP tolerance is likely to be secondary to that of thermal stress (Lucas *et al.* 2013).

Limitations

During all trials, core temperature changed slightly throughout LBNP (Fig. 1), although the magnitude of this change was minimal, except for the core hyperthermia trial when the skin was cooled. We cannot exclude the possibility that a decline in core temperature during the core hyperthermia trial may have improved LBNP tolerance relative to the combined skin and core hyperthermia trial. That said, despite this reduction in core temperature, LBNP tolerance to the core hyperthermia trial remained substantially reduced relative to the control trial.

Perspectives, significance and conclusions

Elevations in internal core temperature that are largely separate from skin temperatures allow a unique insight into the role of core hyperthermia upon LBNP tolerance. Such conditions occur during exercise with adequate evaporative cooling of the skin surface. Likewise, elevations in skin temperature that are largely separate from increased internal core temperatures would allow a unique insight into the role of skin hyperthermia upon LBNP tolerance. Such conditions may be found during a brief exposure to high environmental temperatures. Both skin and core temperatures can increase appreciably in various settings where blood pressure regulation can be compromised owing to the combined effects of increased thermal strain and the physical demands of the occupation, such as in military personnel, firefighters and construction workers, and where the risk of a

haemorrhagic injury is also elevated. For example, during military procedures in hot environments the skin and internal core temperatures can increase to the levels achieved within the present study (Buller *et al.* 2008). As we observed that increases in primarily skin temperature, as well as increases in primarily core temperature, can both reduce tolerance to an LBNP challenge, an increase in both skin and core temperatures is not a prerequisite to reduce tolerance to a haemorrhagic injury. In other words, the ability of individuals to tolerate a haemorrhagic injury is likely to be reduced at any point during day-to-day activities that result in increased skin and/or core temperatures. These data also indicate that any form of body core or skin temperature reduction towards neutral/control temperatures can improve tolerance to a haemorrhagic injury and may therefore be beneficial in the treatment of a haemorrhaging hyperthermic individual in the prehospital setting.

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New Findings

- What is the central question of this study?

  Combined increases in skin and core temperatures reduce tolerance to a simulated haemorrhagic challenge. The aim of this study was to examine the separate and combined influences of increased skin and core temperatures upon tolerance to a simulated haemorrhagic challenge.

- What is the main finding and its importance?

  Skin and core temperatures increase during many occupational settings, including military procedures, in hot environments. The study findings demonstrate that both increased skin temperature and increased core temperature can impair tolerance to a simulated haemorrhagic challenge; therefore, a soldier's tolerance to haemorrhagic injury is likely to be impaired during any military activity that results in increased skin and/or core temperatures.

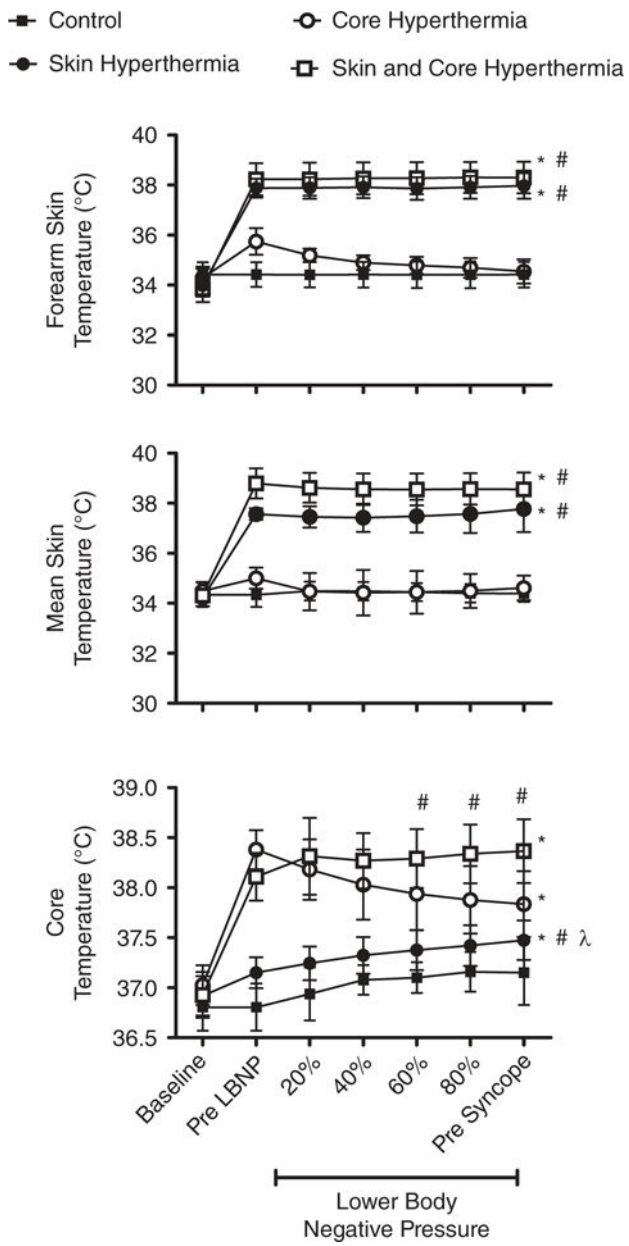

Figure 1. Internal core and mean skin temperatures in each trial prior to and throughout lower-body negative pressure (LBNP) to presyncope

Skin and core temperature responses to the applied thermal conditions and subsequent LBNP to presyncope. Forearm skin temperature was obtained from the site where skin blood flow was assessed. Mean skin temperature is the weighted average of temperatures at six locations. Core temperature was from the ingestible temperature pill. *Different from the control trial (main effect, $P < 0.05$). #Different from the core hyperthermia trial at that respective time point when symbols are placed within the figure or a main effect when the symbol is presented at the side of the figure ($P < 0.05$). λDifferent from the combined skin and core hyperthermia trial (main effect, $P < 0.05$).

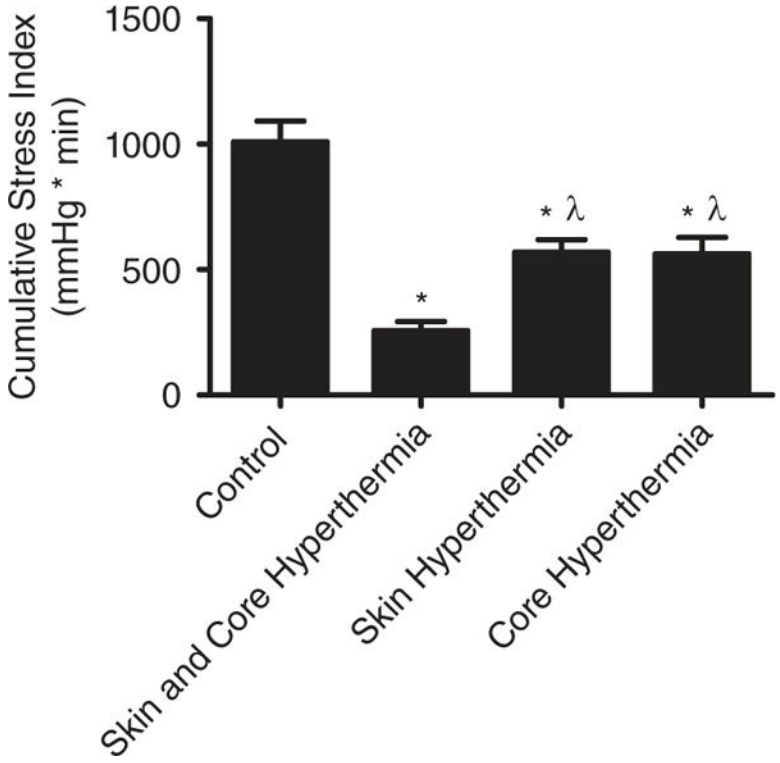

Figure 2. Lower-body negative pressure tolerance expressed as cumulative stress index for each trial

The LBNP tolerance was highest in the control trial. The LBNP tolerance was not different between core hyperthermia and skin hyperthermia trials, but both were higher relative to the combined skin and core hyperthermia trial. *Different from the control trial ($P < 0.05$). $^{\lambda}$Different from the combined skin and core hyperthermia trial ($P < 0.05$).

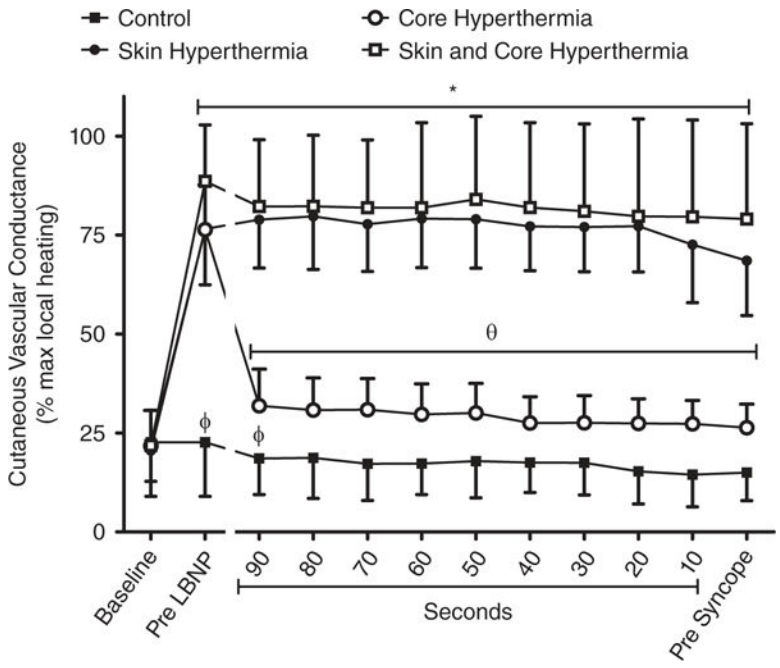

Figure 3. Cutaneous vascular conductance expressed as a percentage of maximum in each trial prior to and throughout the final 90 s of LBNP to presyncope

Cutaneous vascular conductance was elevated to a similar exent relative to baseline in all three heat stress trials compared with the control conditions. During the final 90 s of LBNP, cutaneous vascular conductance remained higher than control values in the skin hyperthermia and combined skin and core hyperthermia trials, but was reduced to control trial values in the core hyperthermia trial. *Different from the control trial ($P < 0.05$). $^{\theta}$Cutaneous vascular conductance in the core hyperthermia trial was different from that in the skin hyperthermia and combined hyperthermia trials ($P < 0.05$). $^{\varphi}$Cutaneous vascular conductance was different between control and core hyperthermia trials at that respective time point ($P < 0.05$).

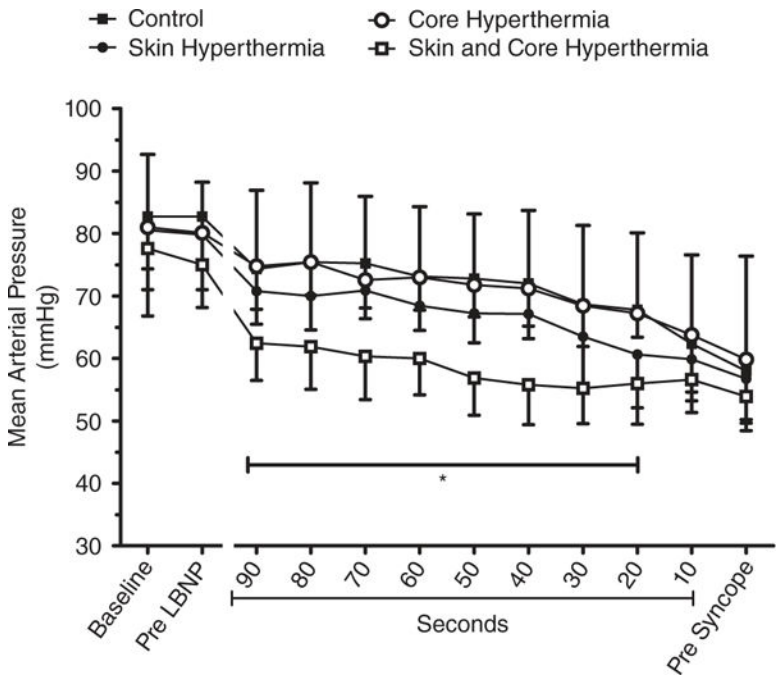

Figure 4. Blood pressure responses to each trial prior to and throughout the final 90 s of LBNP to presyncope

Mean arterial pressure was not different between trials at baseline, pre-LBNP or presyncope. However, mean arterial pressure was lower in the combined skin and core hyperthermia trials relative to both the control and core hyperthermia trials in the time period of 90–20 s prior to presyncope. There were no differences in mean arterial pressure between the skin hyperthermia and the combined skin and core hyperthermia trial at any time point.

*Combined skin and core hyperthermia trial was different from both the control and the core hyperthermia trial ($P < 0.05$).

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Table 1

Haemodynamic and cerebrovascular measurements at baseline, during the applied thermal conditions and at presyncope for each trial

	Control		Skin and core hyperthermia			Skin hyperthermia			Core hyperthermia		
Parameter	**Baseline**	**Pre-LBNP**	**Presyncope**	**Baseline**	**Pre-LBNP**	**Presyncope**	**Presyncope**	**Pre-LBNP**	**Presyncope**	**Baseline**	**Pre-LBNP**	**Presyncope**
Mean arterial pressure (mmHg)	83 ± 12	58 ± 8†	78 ± 11	75 ± 7	54 ± 5*†	81 ± 6	80 ± 5	57 ± 7*†	81 ± 12	80 ± 8	60 ± 17*†
Cardiac output (l min^{-1})	6.7 ± 1.3	—	6.5 ± 1.0	9.7 ± 2.0*‡	—	6.5 ± 0.7	8.2 ± 0.6*‡¶	—	6.8 ± 1.3	8.9 ± 1.6*‡	—
Heart rate (beats min $^{-1}$)	57 ± 10	101 ± 29*	59 ± 13	96 ± 16*	121 ± 30*	58 ± 14	71 ± 7	117 ± 26*†	59 ± 10	77 ± 12	116 ± 20*†
Stroke volume (ml)	106 ± 17	—	111 ± 22	105 ± 28	—	113 ± 14	116 ± 11	—	116 ± 19	107 ± 21*	—
CVC (a.u. $^{-}$ mmHg $^{-1}$)	0.6 ± 0.4	0.4 ± 0.2	0.5 ± 0.2	2.3 ± 0.6*‡	2.1 ± 0.8*‡	0.5 ± 0.2	2.1 ± 0.6*‡	1.9 ± 0.6*‡	0.5 ± 0.3	1.9 ± 0.8*‡¶	0.7 ± 0.3†§
CVC (% max)	23 ± 14	15.0 ± 7.1	22 ± 9	89 ± 14*‡	79 ± 24*‡	21 ± 8	77 ± 14*‡	69 ± 14*‡	22 ± 9	76 ± 11*‡¶	26 ± 6†§
MCAv (cm s^{-1})	68.4 ± 6.4	41.9 ± 8.7*	65.9 ± 8.0	58.4 ± 9.2	36.7 ± 8.9*†	71.2 ± 8.6	63.8 ± 10.7	41.3 ± 12.3*†	67.1 ± 11.6	61.6 ± 14.8	41.00 ± 10.5*†
$P_{\mathrm{ET,CO_2}}$ (mmHg)	43 ± 2	30 ± 8*	44 ± 3	38 ± 6	26 ± 9*†	43 ± 4	40 ± 4	29 ± 5*†	42 ± 4	38 ± 6	29 ± 6*†

Abbreviations: CVC, cutaneous vascular conductance; LBNP, lower-body negative pressure; MCAv, middle cerebral artery blood velocity; and $P_{\mathrm{ET,CO_2}}$, partial pressure of end-tidal carbon dioxide. Values are means ± SD for nine participants, except cardiac output, which is from eight individuals. Mean arterial pressure and CVC data are from nine participants, except at presyncope in both the combined skin and core hyperthermia trial and the core hyperthermia trial, where data are from eight participants.

*Different from baseline within the trial ($P < 0.05$).

†Different from Pre-LBNP within trial ($P < 0.05$).

‡Different from the control trial at that respective time point ($P < 0.05$).

¶Different from the combined skin and core hyperthermia trial at that respective time point ($P < 0.05$).

§Different from both skin hyperthermia and combined skin and core hyperthermia trials within that respective time point ($P < 0.05$).